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1804	

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☐ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), ____ days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice re Patent Drawing, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, Form PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☒ Claims 1-20 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-20 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable. ☐ not acceptable (see explanation or Notice re Patent Drawing, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____ has (have) been ☐ approved by the examiner. ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed on _____, has been ☐ approved. ☐ disapproved (see explanation).

12. ☐ Acknowledgment is made of the claim for priority under U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.

13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

EXAMINER'S ACTION

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as failing to provide an enabling disclosure and an adequate written description of the invention.

Applicants describe the results of experiments in which the expression of HSV-tk from a particular adenoviral vector resulted in reducing the intimal thickness in porcine arteries injured by balloon catheterization, as compared to controls. The data presented is not sufficient to establish enablement for the claimed invention, which encompasses the treatment of any mammal, including humans, with any DNA delivery means containing a thymidine kinase gene. The sole disclosed utility of the method is for therapeutic purposes; however, it is unlikely that others skilled in the art would correlate the data presented in the specification with a therapeutic effect, in view of the small sample size and individual species differences. Also, the animal data does not appear to predict whether or not restenosis is inhibited and not merely delayed, since long-term studies have not been carried out. There is no indication that results of

restenosis-inhibiting experiments in the pig are recognized as being correlatable or predictive as to the inhibition of restenosis in other species of mammal. In fact the Lee et al. article discloses at page 806, column 2, that there are significant species differences between rat, sheep and porcine gene transfer into the arterial wall.

The studies conducted are not predictive of the results of human gene therapy in particular. The Ledley paper, in reviewing somatic cell gene therapy, discusses some of the problems with animal models at page 79. Specifically, the author states:

> While animal experiments are useful for assessing specific aspects of gene transfer, there is no data explicitly supporting the contention that animal experiments can presage the outcome, efficacy, or safety of human applications. The details of anatomy, cell biology, genetics, and immunology of other species do not duplicate the vicissitudes of human biology, particularly when considering retroviral vectors, whose infectiviety, tropism, and pathology is naturally species specific.

The review article by Richard Mulligan states at page 927 that

> it is unclear whether most available animal models will accurately predict either the replicative capacity of adenovirus vectors or their capacity for persistent gene expression in specific human cells in vivo.

Thus, there is no evidence that others skilled in the art would perceive the studies conducted as readily correlatable to those which would be achieved in mammals, generally, nor in humans in particular.

There is no indication that the pig experiment performed by applicants is recognized as being correlatable or predictive as

to the inhibition of restenosis in other species of mammal. In fact the Lee et al. article discloses at page 806, column 2, that there are significant species differences between rat, sheep and porcine gene transfer into the arterial wall.

The specification fails to enable human gene therapy. The Morishita et al. article discloses at page 8474, column 1 that "no effective pharmacological therapy for preventing restenosis in humans has been reported...This failure may reflect the difficulty in identifying appropriate drug targets due to the complexity of the pathophysiological process of neointima formation and/or the inability to deliver sufficient quantities of drugs to the site of injury." At the end of the article, the authors state that "the method of drug delivery is critically important"; holding that the criteria for a successful outcome involved a proper drug target, an efficient drug delivery method and an intraluminal approach. Even given the positive results achieved with their antisense approach, the authors state that the methodology is not yet optimized to allow for clinical use.

The specification fails to adequately describe the cytosine deaminase gene used in the practice of the claimed invention. No sequence is provided and the only description provided by the specification is in the incorporation by reference to non-patent literature, which is improper. See M.P.E.P. § 608.01(p). The specification does not sufficiently disclose how to make vectors encoding the cytosine deaminase gene; nor how to use these

vectors for therapeutic treatment. It would require undue experimentation for one skilled in the art to select appropriate vector materials, the appropriate cytosine deaminase gene sequence for vector insertion, and the appropriate promoters, enhancers and elements necessary to achieve gene expression in therapeutically relevant amounts in view of the highly complex and unpredictable nature of the subject matter.

As to the adenoviral vector employed, the Ad.HSV-tk vector is essential to practice the claimed invention. However, the specification fails to set forth a repeatable process of making the vector, nor is there any indication of deposit of the vector.

Since the vector Ad.HSV-tk is essential to the claimed invention it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the vector is not so obtainable or available, the requirements of 35 U.S.C. §112 may be satisfied by a deposit of the vector. If the deposit is made under the terms of the Budapest treaty, then an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific vector has been deposited under the Budapest Treaty and that the vector will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set

forth in 37 CFR 1.801-1.809, applicants may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that,

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer; and,

(d) the deposit will be replaced if it should ever become inviable.

The specification fails to adequately disclose how to make and use adenoviral vectors in general, non-adenoviral vectors, vector-liposome or vector-ligand conjugates which would be useful for the inhibition of restenosis. For the non-viral transfection means, the specification fails to disclose the appropriate DNA:lipid ratio, and the types of ligands to use. One could not extrapolate the results obtained by applicants to other vectors, as evidenced by Lee et al. (cited by applicants), who compared the results of lipofection with adenoviral vector-mediated gene transfer, and found that "the level of gene transfer resulting from lipofection of the plasmid was far below that obtained with the AviLacA4 vector." See page 806, first paragraph, for example.

The Chapman et al. article and the Takeshita et al. abstract (0903) also disclose some of the other variables involved in

developing strategies for the inhibition of restenosis. Chapman et al. disclose that successful transfection was dependent upon the balloon pressure, the duration of infusion, and the DNA:lipid ratio as well as the perfusion capability of the balloon catheter, since adventitial delivery was not associated with the success of intraluminal delivery. The Takeshita (0903) abstract discloses that DNA:Lipofectin-mediated transfection was far more efficient if administered at 3-14 days post-arterial denudation. They concluded that active cell proliferation augments the efficiency of gene transfer. Active proliferation is required for retroviral-mediated gene transduction; thus, the delivery of the vector at the time of angioplasty or other mechanical damage may be insufficient to transduce a sufficient quantity of cells to achieve the result achieved with the exemplified adenoviral vector.

The specification is not considered enabling for any and all "mechanical means" of injury, since different treatments may result in differences in arterial injury. Thus, although applicant has disclosed that following balloon catheterization, the proliferation profile reflected in Fig. 2 is in effect, such may not hold for laser, stent, or other means of injury. The Santoian et al. abstract is cited to provide support for this reasoning. Specifically, Santoian et al. compared the neointimal patterns which occurred following balloon injury, reinjury or stent injury. The investigators found that the site of intimal

hyperplasia as well as the degree of intimal thickness varied depending upon the procedure employed. The Lee et al. reference, cited by applicants, discloses at page 806 that even within a given procedure (i.e., balloon catheterization), differing degrees of vessel wall necrosis was the likely cause of the widely differing gene transfer efficiencies. Thus, one skilled in the art could not reasonably correlate the results set forth in the specification with those that would be expected by other mechanical injury means.

It is therefore concluded that in light of the quantity of experimentation necessary, the lack of adequate direction or guidance presented, the lack of correlatable working examples, the nature of the invention, the state of the prior art with its recognized unpredictability, and the breadth of the claims, it would require undue experimentation for others skilled in the art to practice the invention.

Claims 1-20 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-20 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claims 1 and 16, the phrase "preferentially incorporating" is vague and indefinite as to what is intended; i.e., is the incorporating step performed by the

artisan or by the nucleoside analog? In claim 4, it is believed that "is in a viral vector" should be "is a viral vector". Claim 7 and 18 fail to distinctly claim what applicant regards as the invention, since in light of the specification, plural elements, signals and origins of replication are not intended. The phrase "other necessary adenoviral genes" is indefinite as to exactly what is encompassed. As to claims 12 and 13, there is no antecedent basis in claim 1 for "said suicide compound" or for "said modification". In claim 18, the phrase "about 9 map units" is vague and indefinte as to its metes and bounds, since it is unclear from the specification how much of the genome other than 9.2 map units from the 5' end could be deleted. In claim 20, it is unclear by the recitation "said elements" which element in the independent claim is being referred to.

35 U.S.C. § 101 reads as follows:

> "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title".

Claims 1-20 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility. The sole utility of the claimed invention is directed to therapy. Others skilled in the art are unlikely to accept the allegations of therapeutic utility on their face in light of the contemporary knowledge in the art, as discussed in the rejection under 35 U.S.C. § 112 above.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> > (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 18-19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Haj-Ahmad et al. The Haj-Ahmad et al. article discloses the construction of an E1, E3 deleted adenoviral vector containing the HSV-tk gene and essential elements as claimed herein. The claimed subject matter is thus anticipated by the prior art.

The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103,

the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103.

Claims 1, 2 and 12-15 are rejected under 35 U.S.C. § 103 as being unpatentable over Takeshita et al. (abstract 3179) in view of Plautz et al.

The Takeshita et al. abstract discloses DNA-liposome-mediated gene transfer into rabbit atherosclerotic arteries. Gene expression was indicated and the treated lesions showed a reduction in restenosis. Thus, the Takeshita et al. abstract discloses the claimed invention, with the exception that the HSV-tk gene was not employed.

However, one of ordinary skill in the art would have been motivated to substitute the HSV-tk gene for that of the prior art, given its known benefit in vivo as evidenced by Plautz et al. for the selective lysis of rapidly proliferating cells upon ganciclovir treatment. Since this proliferation is the hallmark of restenosis, it would have been obvious to reduce the formation of neointima by the claimed approach.

Claims 16-17 are rejected under 35 U.S.C. § 103 as being unpatentable over Takeshita et al. (abstract 3179) in view of Plautz et al. and further in view of Mullen et al. The Mullen et al. reference discloses the introduction of a polynucleotide comprising a cytosine deaminase gene which enables the

transfected cells to be eliminated by 5-fluorocytosine. At page 36, the authors state that the system could be used in vivo in gene transfer therapies for the selective elimination of the genetically engineered cells. Since the authors suggest that the herpes simplex thymidine kinase gene operates in an analogous fashion, the substitution of tihe CD system disclosed by Mullen et al. for the HSV-tk system of the prior art would have been obvious to one of ordinary skill in the art at the time the invention was made.

Claims 3-5 and 8 are rejected under 35 U.S.C. § 103 as being unpatentable over Takeshita et al. (abstract 3179) in view of Plautz et al. as applied to claims 1, 2 and 12-15 above, and further in view of Willard et al. The combination of Takeshita et al. and Plautz et al. does not suggest the use of an adenoviral vector for the purpose of expressing the HSV-tk gene.

However, one of ordinary skill in the art would have been motivated to substitute an adenoviral vector for the delivery means of the prior art in view of Willard et al. who discloses the advantages of adenoviral vectors over the direct DNA approach. The claimed invention would have therefore been obvious to one of ordinary skill in the art at the time the invention was made.

Claims 9 and 11 are rejected under 35 U.S.C. § 103 as being unpatentable over Takeshita et al. (abstract 3179) in view of Plautz et al. as applied to claims 1, 2 and 12-15 above, and

further in view of Willard et al. and Curiel et al. Willard et al. disclose the advantages of adenoviral vectors over the direct DNA approach. The Curiel et al. reference discloses that adenovirus enhances the transfer of DNA complexed to transferrin-polylysine conjugates, thus providing the motivation to employ the combined system of the claims. Thus, the claimed method involving the complexation of a vector with a receptor ligand would have been obvious to one of ordinary skill in the art at the time the invention was made.

Claims 6 and 20 are rejected under 35 U.S.C. § 103 as being unpatentable over Takeshita et al. (abstract 3179) in view of Plautz et al. as applied to claims 1, 2 and 12-15 above, further in view of Willard et al. and Herbomel et al. The Herbomel et al. reference discloses the presence of two enhancers in polyoma virus which can be employed to regulate heterologous marker gene expression and which greatly enhanced collagen promoter activity when placed upstream of the transcriptional start site (see page 657, column 1). Moreover, the enhancer A was found to be homologous to the adenoviral E1a enhancer. It would have therefore been obvious to employ a polyoma virus enhancer in the claimed method for the expected result of enhancing transcription in the claimed vector. The claimed invention would have therefore been obvious to one of ordinary skill in the art at the time the invention was made.

No claim is allowed.

Any inquiry concerning this communication should be directed to Examiner Stone at telephone number (703) 308-0196.

Jacqueline Stone

August 4, 1994

JACQUELINE STONE
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ART UNIT 1804